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Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285
U.S.A.

Phone 317 276 2000

Dockets Management Branch
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

RE: Docket #199D-0529

Dear Sir or Madam:

Eli Lilly and Company would like to comment on the recently released Guidance *Changes to an Approved NDA or ANDA; Specifications – Use of Enforcement Discretion for Compendial Changes* (November 2004). This guidance represents an improvement over the provision in the guidance released in April of 2004, *Changes to an Approved NDA or ANDA*, where section C.1.e. states, per 21 CFR 314.70(c)(2)(iii), that a Changes Being Effected in 30 Days (CBE 30) supplement is required for:

> Relaxing an acceptance criterion or deleting a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements (314.70(c)(2)(iii)).

The November 2004 guidance states:

> FDA intends to exercise enforcement discretion and does not intend to take action to enforce compliance with the compendial changes requirement as stated in 21 CFR 314.70(c)(2)(iii) if manufacturers submit such changes in their annual reports. FDA intends to develop further guidance to clarify the requirements of 21 CFR 314.70(c)(2)(iii).

The new guidance is an improvement in that such a change made to comply with a USP/NF change is annual reportable rather than requiring a CBE 30 submission. What should be noted is that until the recent revision of 314.70 this type of change was not reportable at all. It should also be noted that per the FD&C Act, regulated industry is required to comply with the current provisions of the USP/NF Monographs for both excipients and Active Pharmaceutical Ingredients (APIs). Eli Lilly and Company is in agreement that changes of this type for APIs potentially represent a risk and concur that they should be reported in the Annual Report in this case.

Where we do not agree is in the case involving monograph changes for excipients. If a monograph is changed to add a new test or tighten acceptance criteria for an excipient, then users of that material are required to ensure that it meets the modified monograph under existing cGMPs. What is the public health risk that you seek to address by this new requirement? We assume that it is simply this: it is possible that an excipient may no longer be suitable for a specific purpose if an acceptance criterion is relaxed or a test is dropped. That is, it may no longer be suitable for use in a *specific* drug product.

We would like to point out that the modification of compendial monographs is an open process during which both industry and the Agency have the opportunity comment on the appropriateness of changes before they are implemented in the USP/NF. In the instance described above, we would like to inquire how the reviewer will be able to know that a broader acceptance range for a test or dropping a test will be likely to lead to the material not being appropriate for a specific use? And if a reviewer is able to raise this concern, shouldn't that happened during the public comment period on the proposal to change the monograph? Certainly, if we are aware that a modification of an excipient monograph would create a situation where the material is likely not to be suitable for use in one of our approved drug products, we would be under obligation to raise that concern during the comment period, and we would do so.

It should be pointed out that the approach taken in the revised 314.70, the April 2004 Changes guidance and the November 2004 guidance represents both a potentially significant additional regulatory burden for industry and a similarly significant drain on Agency resources. When an excipient monograph is revised to either drop a test or broaden an acceptance criterion, it is possible that the change will have to be noted in numerous annual reports, all of which will have to be reviewed by Agency staff.

That this is a cGMP requirement that is currently enforced by FDA field investigators can be seen from the following examples regarding excipients obtained through Freedom of Information requests:

Metuchen Analytical, Inc. received a 483 observation on 4/25/1997 for testing Povidone USP by a method from USP 22 rather than USP 23, which was then current.
Michigan Biologic Products Institute was cited on 2/20/1998 for failure to address raw material monograph updates.

- Thames Pharmacal Company received a Warning Letter, dated 12/17/1999, in part for its failure to perform tests according to current USP monograph methods.
- Scientech Laboratories, Inc. received a Warning Letter, dated 6/26/2000, among whose citations was the firm's failure to adhere to compendial monograph testing for Magnesium Stearate and Potassium Chloride.

Thus it can be seen that the requirement to follow current compendial monographs is a cGMP issue and has been enforced by the Agency in this way. The revised 21 CFR 314.70(c)(2)(iii), the April 2004 Changes guidance, and the November 2004 modification of that guidance have made a revision that causes this now to be a review

concern in the specific instance where an excipient monograph is changed to relax an acceptance criterion or delete a test.

It is our understanding that the Agency is currently in the process of developing the additional guidance in a question and answer format regarding the general topic of changes to approved applications.

Eli Lilly and Company would like to offer a suggestion for this guidance that we believe properly addresses the risks from compendial revisions of excipient monographs and the associated regulatory burden. The following question and answer propose addressing the concern properly: cGMP obligation for all firms to ensure that an the excipient whose monograph has been modified remains suitable for its intended use, and annual report notification *only* in those cases where it is determined that the dropped test or tighter acceptance criterion are essential to ensure that this is so.

> Question: Please clarify Agency expectations regarding the situation where an official compendium has revised an excipient monograph to either drop a test or broaden an acceptance criterion. The revised 21 CFR 314.70(c)(2)(iii) and the April 2004 Changes guidance both state that a CBE 30 supplement is required. However, the November 2004 Changes guidance indicates that enforcement discretion will be used to permit submitting such changes in the annual report.
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> Answer: After careful consideration the Agency has determined that the key concern here is the suitability of the excipient for its intended use. There is a risk that, if a test, previously required by the excipient monograph, is dropped, or if an acceptance criterion is broadened, the excipient may meet the new monograph requirements but not be suitable for its intended use. It is incumbent on the firm using the excipient to ensure that adoption of any monograph changes will provide continued assurance of the quality and suitability of the excipient (21 CFR 211.84(d)(2) and 211.84(e)).
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> Therefore it is the expectation of the Agency that changes to excipient monographs where an acceptance criterion is broadened or a test is dropped normally be addressed by a firm's quality system ensuring that the excipient will remain suitable for it's intended use with no additional reporting to the Agency required. In those specific instances where a firm determines that broadening an acceptance criterion or dropping a monograph test to comply with an official compendium will not provide sufficient assurance of an excipient's suitability for a particular use, the maintenance of the narrower acceptance criterion or use of a specific test for that excipient for that use should be reported in the appropriate Annual Report.
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> However, in the case of a monograph change for drug substance, the November 2004 guidance still represents current Agency thinking: *all* such changes to comply with compendial changes to drop a test or broaden an acceptance criterion should be reported; the Agency will exercise enforcement discretion if

those changes are reported in an annual report rather than in a Changes Being Effected in 30 Days (CBE 30) supplement.

Eli Lilly and Company appreciates the opportunity to comment on this issue and looks forward to an appropriate resolution of the issue we have raised in this letter.

Sincerely,

Robert H. Seevers, Ph.D.
Technical Advisor
Global Manufacturing Site Regulatory Affairs

cc
John Simmons, Ph.D.
Director, Office of New Drug Chemistry Division I
WOC2
1451 Rockville Pike
Rockville, MD 20852

David Cummings
Office of Pharmaceutical Science
Rockwall II
5515 Security Ln.
Rockville, MD 20852

Larry Ouderkirk
Office of Pharmaceutical Science
Rockwall II
5515 Security Ln.
Rockville, MD 20852